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(54) Title: METHODS FOR MONITORING AND GUIDING THERAPEUTIC SUPPRESSION OF PARATHYROID HORMONE
IN RENAL PATIENTS HAVING SECONDARY HYPERPARATHYROIDISM

(57) Abstract: The present invention relates to novel methods for monitoring and guiding therapeutic suppression of parathyroid hormone in renal patients having secondary hyperparathyroidism. One determines and monitors the level of parathyroid hormone agonist and parathyroid hormone antagonist in the renal patient. The parathyroid hormone suppressing therapeutic is administered to the patient so as to minimize the level of parathyroid hormone antagonist.

**METHODS FOR MONITORING AND GUIDING THERAPEUTIC SUPPRESSION
OF PARATHYROID HORMONE IN RENAL PATIENTS HAVING SECONDARY
HYPERPARATHYROIDISM**

5 CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is related to U.S. Patent Application No. 10/002,818, filed November 2, 2001, now allowed, which is incorporated herein by reference.

TECHNICAL FIELD

[0002] The present invention relates to novel methods for monitoring and guiding
10 therapeutic suppression of parathyroid hormone in renal patients having secondary hyperparathyroidism. One determines and monitors the level of parathyroid hormone agonist and parathyroid hormone antagonist in the renal patient. The parathyroid hormone suppressing therapeutic is administered to the patient so as to minimize the level of parathyroid hormone antagonist.

15 BACKGROUND ART

[0003] Calcium plays an indispensable role in cell permeability, the formation of bones and teeth, blood coagulation, transmission of nerve impulse, and normal muscle
20 contraction. The concentration of calcium ions in the blood is, along with calcitriol and calcitonin, regulated mainly by parathyroid hormone (PTH). Although calcium intake and excretion may vary, PTH serves through a feedback mechanism to maintain a steady concentration of calcium in cells and surrounding fluids. When serum calcium lowers, the parathyroid glands secrete PTH, affecting the release of stored calcium. When serum calcium increases, stored calcium release is retarded through lowered secretions of PTH.

[0004] The complete form of human PTH, sometimes referred to in the art as hPTH
25 but referred to in the present invention as an example of PTH agonist, is a unique 84 amino acid peptide (SEQ ID NO:1), as is shown in FIGURE 1. Researchers have found that this peptide has an anabolic effect on bone that involves a domain for protein kinase C activation (amino acid residues 28 to 34) as well as a domain for adenylate cyclase activation (amino acid residues 1 to 7). However, various catabolic forms of clipped or fragmented PTH
30 peptides also are found in circulation, most likely formed by intraglandular or peripheral metabolism. For example, whole PTH can be cleaved between amino acids 34 and 35 to produce a (1-34) PTH N-terminal fragment and a (35-84) PTH C-terminal fragment.

Likewise, clipping can occur between either amino acids 36 and 37 or 37 and 38. Recently, a large PTH fragment referred to as "non-(1-84) PTH" has been disclosed which is clipped closer to the N-terminal end of PTH. (See R. LePage *et al.*, "A non-(1-84) circulating parathyroid hormone (PTH) fragment interferes significantly with intact PTH commercial assay measurements in uremic samples," Clin. Chem. (1998); 44: 805-810.)

[0005] The clinical need for accurate measurement of PTH is well demonstrated. Serum PTH level is one of the most important indices for patients with the following diseases: familial hypocalciuria; hypercalcemia; multiple endocrine neoplasia types I and II; osteoporosis; Paget's bone disease; primary hyperparathyroidism -caused by primary hyperplasia or adenoma of the parathyroid glands; pseudohypoparathyroidism; and renal failure, which can cause secondary hyperparathyroidism.

[0006] PTH plays a role in the course of disease in a patient with chronic renal failure. Renal osteodystrophy (RO) is a complex skeletal disease comprising osteitis fibrosa cystica (caused by PTH excess), osteomalacia - unmineralized bone matrix (caused by vitamin D deficiency), extraskelatal calcification/ossification (caused by abnormal calcium and phosphorus metabolism), and adynamic low bone turnover disease (contributed to by PTH suppression). Chronic renal failure patients can develop RO. Failing kidneys increase serum phosphorus hyperphosphoremia) and decrease 1,25-dihydroxyvitamin D (1,25-D) production by the kidney. The former results in secondary hyperparathyroidism from decreased gastrointestinal calcium absorption and osteitis fibrosa cystica from increased PTH in response to an increase in serum phosphorus. The later causes hypocalcemia and osteomalacia. With the onset of secondary hyperparathyroidism, the parathyroid gland becomes less responsive to its hormonal regulators because of decreased expression of its calcium and vitamin D receptors. Serum calcium drops. RO can lead to digital gangrene, bone pain, bone fractures, and muscle weakness.

[0007] For chronic renal failure patients with secondary hyperparathyroidism, a number of different therapeutic treatments are available. One can administer calcium carbonate so as to directly adjust the available calcium ion level. However, with the increasing incidence of ectopic calcification, increasing calcium intake is often not desirable. One can administer calcimimetics, such as AMG073 made by Amgen, Inc. of Thousand Oaks, California. However, AMG073 has not been approved for use in the USA . One can administer vitamin D analogues, (such as the Calcijex® or Zemplar® brands made by Abbott Labs of Abbott Park, Illinois; Rocaltrol® brand made by Roche Laboratories of Basle, Switzerland; Oxarol brand made by Chugai Pharmaceutical), so as to lower PTH. However,

researchers have found that vitamin D analogues can oversuppress PTH, thereby leading to adynamic low bone turnover disease setting the patient at risk of ectopic and vascular calcification. (See the package insert for Zemplar®, Abbott Reference 06-9998-R1-Rev, April 1998. See the package insert for Rocaltrol®, Roche Laboratories, inc. November 1998

5 Product identification Guide, page 334.)

[0008] Researchers have also found that a large circulating PTH fragment (e.g., cyclase inactive parathyroid hormone) functions as a naturally occurring PTH antagonist. Cyclase inactive PTH has been found to be useful, alongside whole PTH, as an indicator in separating untreated end stage renal disease (ESRD) patients with high bone turnover from
10 those with adynamic low bone turnover. (See Faugere, M. C. *et alia*. "Improved Assessment of Bone Turnover by the PTH 1-84/large C-PTH fragments ratio in ESRD patients", Kidney International 2001; 60: 1460-1468.) Moreover, researchers have found that cyclase inactive PTH can cause adynamic low bone turnover by inhibiting the formation of osteoclasts, bone resorption, and bone turnover. (See Divieti, P. *et alia*, "In vitro Inhibition of Bone Resorption
15 by Human PTH (7-84)" J. Bone Miner Res 2001:Suppl 1, S307. See also Faugere, M.C. *et alia*, "The Effects of PTH (1-84) on bone turnover are Antagonized by PTH (7-84) in Thyroparathyroidectomized and Nephrectomized Rats"; J Am Soc Nephrol 12:2001, 764A.)

[0009] Determining circulating biologically active PTH levels in humans has been challenging. One major problem is that PTH is found at low levels, normally 10 pg/mL to 65
20 pg/mL. Coupled with extremely low circulating levels is the problem of the heterogeneity of PTH and its many circulating fragments. In many cases, immunoassays have faced substantial and significant interference from circulating PTH fragments. For example, some commercially available PTH kits have almost 100% cross-reactivity with the non- (1-84) PTH fragment, (see the LePage article).

25 [0010] PTH immunoassays have varied over the years. One early approach is a double antibody precipitation immunoassay found in U. S. 4,369,138 to Arnold W. Lindall *et alia*. A first antibody has a high affinity for a (65-84) PTH fragment. A radioactive labeled (65- 84) PTH peptide is added to the sample with the first antibody to compete for the endogenous unlabeled peptide. A second antibody is added which binds to any first antibody
30 and radioactive labeled PTH fragment complex, thereby forming a precipitate. Both precipitate and supernatant can be measured for radioactive activity, and endogenous PTH levels can be calculated therefrom.

[0011] In an effort to overcome PTH fragment interference, immunoradiometric two-site assays for intact PTH (I-PTH) have been introduced, such as Allegro® Intact PTH assay

by the Nichol's Institute of San Juan Capistrano, California. In one version, a capture antibody specifically binds to the C-terminal portion of hPTH while a labeled antibody specifically binds to the N-terminal portion of the captured hPTH. In another, two monoclonal antibodies were used, both of which attached to the N-terminal portion of hPTH.

- 5 Unfortunately, these assays have problems in that they measure but do not discriminate between whole PTH and non-whole PTH peptide fragments. This inability comes to the fore in hyperparathyroid patients and renal failure patients who have significant endogenous concentrations of large, non-whole PTH fragments.

- [0012] Recently, Scantibodies Laboratory, Inc. of Santee, California USA introduced
10 a series of novel kits that allow for the accurate measurement of both PTH agonist and PTH antagonist. The PTH agonist assay is a direct measurement, while the PTH antagonist assay is a calculated value from the difference of the PTH agonist assay value and a total PTH (including both PTH agonist and PTH antagonist) assay value. A number of unexpected advantages have become available to the physician, including the first non-invasive method
15 for assisting in the differentiation of secondary hyperparathyroid patients with HBT and ALBT.

DISCLOSURE OF THE INVENTION

- [0013] In one embodiment, a method is provided for monitoring and guiding therapeutic suppression of parathyroid hormone in renal patients having secondary
20 hyperparathyroidism comprising: a) determining and monitoring the level of parathyroid hormone (PTH) agonist in a renal patient having secondary hyperparathyroidism; b) determining and monitoring the level of PTH antagonist in the patient; and c) administering a therapeutic to the patient that suppresses PTH agonist whereby the amount of therapeutic administered is adjusted such that the level of PTH antagonist is minimized. Frequently, the
25 therapeutic is administered in increasing increments from a nominal amount. In addition, frequently steps a) and b) are performed using a sample obtained from a renal patient, which sample may be a serum, plasma and/or blood sample.

- [0014] In one aspect the renal patient is already receiving the therapeutic, and therapeutic administration is terminated for a time sufficient to allow the patient to return to
30 at least a relatively non-suppressed state. In one aspect, this timing may be measured with respect to parathyroid gland status and/or bone status. Relatedly, the time sufficient to allow the patient to return to at least a relatively non-suppressed state is frequently between about three months to about six months, with respect to bone status. The time sufficient to allow

the patient to return to at least a relatively non-suppressed state is frequently between about three minutes to about twenty minutes, with respect to parathyroid gland status. On occasion, the time sufficient to allow the patient to return to at least a relatively non-suppressed state is between about two weeks to about six weeks, or sometimes about four weeks. In addition, while guiding therapy of these patients, the amount of administered therapeutic may be adjusted until the level of PTH antagonist is minimized.

[0015] In another aspect of the present invention the therapeutic being administered is selected from the group consisting of calcium, vitamin D, vitamin D analogues, and calcimimetics (e.g., AMG073). Frequently, when vitamin D analogs are used, they may be selected from paricalcitol, calcitriol, maxacalcitol, alfacalcidol, calcifediol, or ergocalciferol.

[0016] In a further aspect of the present invention, the PTH agonist level is compared with the PTH antagonist level. In another aspect, the PTH agonist level is compared with the total parathyroid hormone level. In yet another aspect, the PTH antagonist level is compared with the total parathyroid hormone level. In a further aspect, the PTH agonist level is compared with the PTH antagonist level in the form of a ratio or proportion.

[0017] In one aspect, the PTH antagonist level is determined by determining a total PTH level and determining a PTH agonist level followed by subtracting the PTH agonist level from the total PTH level.

[0018] In another aspect, the PTH agonist level and the PTH antagonist level are determined using an immunoassay. In yet another aspect, the PTH agonist level is determined using an antibody that distinguishes PTH agonist from PTH antagonist. In a further aspect, frequently the PTH antagonist level is determined using an antibody that distinguishes PTH agonist from PTH antagonist.

[0019] In one embodiment, the method above may further comprise monitoring for vascular calcification in the patients. Frequently, vascular calcification is monitored by monitoring alkaline phosphatase levels in the patient.

[0020] In another embodiment, the PTH agonist levels and the PTH antagonist levels are compared, individually or together, with corresponding bone biopsy data. In one aspect, the ratio or proportion of PTH agonist to PTH antagonist will be compared with corresponding bone biopsy data. On occasion, bone biopsy data will be used to verify the results of PTH agonist level and/or PTH antagonist level determinations and/or PTH agonist/antagonist ratios. Frequently, the PTH agonist level and the PTH antagonist level determinations are compared with corresponding bone biopsy data after administration of the therapeutic. On occasion, this comparison after administration of the therapeutic is useful to

monitor the PTH therapy of patients. Frequently, such treatment is directed to decreasing PTH agonist levels and minimizing PTH antagonist levels.

[0021] In a further aspect, the PTH agonist comprises a contiguous portion of human PTH having an amino acid sequence set forth in SEQ ID NO:1 (PTH₁₋₈₄), and the PTH agonist has the following characteristics: the N-terminal amino acid residue of the PTH agonist starts at position 1 of the PTH₁₋₈₄; and the C-terminal amino acid residue of the PTH agonist ends at any position spanning position 34 through position 84 of the PTH₁₋₈₄. In another aspect, the PTH antagonist comprises a contiguous portion of human PTH having an amino acid sequence set forth in SEQ ID NO:1 (PTH₁₋₈₄), and the PTH antagonist has the following characteristics: the N-terminal amino acid residue of the PTH antagonist starts at any position spanning position 2 through position 33 of the PTH₁₋₈₄; the C-terminal amino acid residue of the PTH antagonist ends at any position spanning position 35 through position 84 of the PTH₁₋₈₄; and the PTH antagonist has a minimal length of three amino acid residues.

[0022] In another embodiment, a method is provided for monitoring and guiding therapeutic suppression of parathyroid hormone in renal patients having secondary hyperparathyroidism comprising: a) obtaining a sample from a renal patient having secondary hyperparathyroidism; b) determining and monitoring the level of PTH antagonist in the renal patient; and c) administering a therapeutic to the patient capable of suppressing a PTH agonist, whereby the amount of therapeutic administered is adjusted such that the level of PTH antagonist is minimized in the patient.

[0023] In a further embodiment, kits are provided that are useful for monitoring and guiding therapeutic suppression of parathyroid hormone in renal patients having secondary hyperparathyroidism comprising: a) means for monitoring the level of parathyroid hormone (PTH) agonist in a renal patient having secondary hyperparathyroidism; b) means for monitoring the level of PTH antagonist in the patient; and c) means for administering a therapeutic to the patient that suppresses PTH agonist whereby the amount of therapeutic administered is adjusted such that PTH agonist levels are decreased and the level of PTH antagonist is minimized.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] FIGURE 1 is a diagrammatic view of human wPTH.

[0025] FIGURE 2 is a graph comparing PTH measurement parameters over time for patients receiving a PTH suppressant therapy.

DETAILED DESCRIPTION OF THE INVENTION

[0026] For clarity of disclosure, and not by way of limitation, the detailed description of the invention is divided into the subsections that follow.

A. Definitions

5 [0027] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. All patents, applications, published applications and other publications referred to herein are incorporated by reference in their entirety. If a definition set forth in this section is contrary to or otherwise inconsistent with a definition set forth in the patents,
10 applications, published applications and other publications that are herein incorporated by reference, the definition set forth in this section prevails over the definition that is incorporated herein by reference.

[0028] As used herein, "a" or "an" means "at least one" or "one or more."

[0029] As used herein, "parathyroid hormone (PTH) agonist" refers to the complete
15 molecule of PTH or a fragment, derivative or analog thereof that stimulates osteoclasts formation and bone turnover to increase blood calcium levels. PTH agonist further refers to peptides which have PTH agonist properties. Other names of PTH include parathormone and parathyrin. For purposes herein, the name "parathyroid hormone (PTH)" is used herein, although all other names are contemplated. It is intended to encompass PTH agonist with
20 conservative amino acid substitutions that do not substantially alter its biological activity. Suitable conservative substitutions of amino acids are known to those of skill in this art and may be made generally without altering the biological activity of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see, e.g.,
25 Watson et al., MOLECULAR BIOLOGY OF THE GENE, 4th Edition, 1987, The Benjamin/Cummings Pub. Co., p.224). PTH agonist assay values may be obtained by measuring a sample with a Scantibodies Whole PTH Assay or a Scantibodies CAP Assay or a 3rd generation PTH Assay or a Nichols BioIntact PTH assay or an Immunotopics Human Bioactive PTH assay. "Cyclase activating PTH," "whole PTH," and "CAP" are
30 representative examples of PTH agonists.

[0030] As used herein, "parathyroid hormone (PTH) antagonist" refers to a PTH fragment or derivative that counters the effect of a PTH agonist or otherwise lacks PTH agonist activity. It is intended to encompass PTH antagonist with conservative amino acid

substitutions that do not substantially alter its activity. Suitable conservative substitutions of amino acids are known to those of skill in this art and may be made generally without altering the biological activity of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see, e.g., Watson, et al. MOLECULAR BIOLOGY OF THE GENE, 4th Edition, 1987, The Benjamin/Cummings Pub. co., p.224). "Cyclase inactive PTH" and "CIP" are representative examples of PTH antagonists.

[0031] As used herein, the terms "total PTH," "intact PTH" and "total intact PTH" are interchangeable and refer to an assay directed at measuring PTH agonist and PTH antagonist levels.

[0032] As used herein, a "functional derivative or fragment" of PTH agonist or PTH antagonist refers to a derivative or fragment of PTH that still substantially retains its function as a PTH agonist or PTH antagonist. Normally, the derivative or fragment retains at least 50% of its PTH agonist or PTH antagonist activity. Preferably, the derivative or fragment retains at least 60%, 70%, 80%, 90%, 95%, 99% and 100% of its PTH agonist or PTH antagonist activity. It is also possible that a functional derivative or fragment of PTH agonist or PTH antagonist has higher PTH agonist or PTH antagonist activity than a parent molecule from which the functional derivative or fragment is derived from.

[0033] As used herein, "treatment" means any manner in which the symptoms of a condition, disorder or disease are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein.

[0034] As used herein, "disease or disorder" refers to a pathological condition in an organism resulting from, e.g., infection or genetic defect, and characterized by identifiable symptoms.

[0035] As used herein, "adynamic low bone turnover disease" refers to a variety of disorders involving abnormal PTH agonist and/or antagonist levels in a person. This definition is non-limiting in that it does not refer to only one specific disease, it refers to a variety of disorders that may result from abnormal PTH or PTH component levels in a person. As PTH levels are tied to bone turnover rate, abnormally low levels of PTH agonist, abnormally low levels of PTH agonist/antagonist ratios, and abnormally high levels of PTH antagonist may lead to abnormally low bone turnover in a person. In a person, this type of state may indicate the presence of, or susceptibility to, an adynamic low bone turnover disease. Conversely, abnormally high levels of PTH agonist, abnormally high levels of PTH

agonist/antagonist ratios, and abnormally low levels of PTH antagonist may lead to abnormally high bone turnover in a person.

[0036] As used herein the term "sample" refers to anything which is suspected of containing an analyte for which an analyte assay is desired. The sample may be a biological sample, such as a biological fluid or a biological tissue. Examples of biological fluids include urine, blood, plasma, serum, saliva, semen, stool, sputum, cerebral spinal fluid, tears, mucus, amniotic fluid or the like. Biological tissues are aggregate of cells, usually of a particular kind together with their intercellular substance that form one of the structural materials of a human, animal, plant, bacterial, fungal or viral structure, including connective, epithelium, muscle and nerve tissues. Examples of biological tissues also include organs, tumors, lymph nodes, arteries and individual cell(s). Frequently, samples obtained for use in the present invention contain, or are suspected of containing, levels of PTH agonist and/or PTH antagonist that are detectable through methods described and contemplated herein.

[0037] As used herein, the term "vitamin D analog" refers to any available source of synthetic vitamin D from a variety of sources for clinical or experimental use. For example, vitamin D analogs may be obtained from sources such as Abbott Laboratories, Bone Care International, Hoffman-La Roche, Ltd., Chugai Pharmaceutical Co., Amgen, Inc., NPS Pharmaceuticals, Inc, Kirin Brewing Company, Ltd., Sumitomo Corp., etc. Examples of vitamin D analogs available from these sources include Calcijex®, Zemplar®, Hectoral®, Rocaltrol®, Oxarol, etc. In addition, the active ingredients in a variety of synthetic vitamin D sources contemplated herein may include paricalcitol, calcitriol, maxacalcitol, alfacalcidol, calcifediol, or ergocalciferol.

B. Risk and therapy determinations based on PTH agonist levels and PTH antagonist levels

[0038] The present invention relates to novel methods for monitoring and guiding therapeutic suppression of parathyroid hormone in renal patients having secondary hyperparathyroidism. In one aspect, one determines and monitors the level of PTH agonist and PTH antagonist in the renal patient. In another aspect, one determines and monitors the level of PTH agonist in the renal patient. Frequently, the parathyroid hormone suppressing therapeutic is administered to the patient so as to minimize the level of PTH antagonist.

[0039] Secondary hyperparathyroidism is a common disease in renal compromised patients, especially those with ESRD. Virtually all ESRD patients have bone disease and mineral metabolism disorders, either high bone turnover disease or adynamic low bone

turnover disease. Elevated levels of PTH agonist (with respect to PTH antagonist) lead to high bone turnover disease (HBT). Elevated levels of PTH antagonist (with respect to PTH agonist) lead to adynamic low bone turnover disease (ALBT). In general, the more medically serious of these two disorders is ALBT due to the higher risk of soft tissue calcification that accompanies this disorder. In ALBT ectopic tissue calcification results in vascular stenosis (including occlusion of coronary arteries) and aortic rigidity. Therefore, ALBT patients are subject to a higher likelihood of serious medical complications due to a circulatory system failure, such as myocardial infarction than those with HBT. One reason for this is that it has been difficult in the past to find a reliable therapeutic treatment for ALBT. In addition, the use of therapeutic PTH suppression can lead to therapeutic PTH over-suppression which, in turn, leads to ALBT. In other words, due to the lack of a reliable indicator, PTH agonist suppressant therapy can inadvertently lead to ALBT due to PTH over-suppression.

[0040] Difficulty with implementing PTH suppression therapy can be seen in the setting of at least ten different PTH target recommendations within the past decade. The net result of this uncertainty in therapeutic indicators is that the incidence of vascular calcification has been reported to be 88% for ESRD patients. (See Goodman, W. et al., "Coronary Artery Calcification in Young Adults with End Stage Renal Disease Who Are Undergoing Dialysis"; NEJM 2000, May 18; 342:20, 1478-1483.)

[0041] A novel finding leading to the present invention is that while the PTH agonist level decreases in response to the administration of PTH agonist suppressants, PTH antagonist levels may not. Moreover, oversuppression through the use of PTH agonist suppressants may increase the PTH antagonist level. For an untreated renal patient with an elevated PTH agonist level, the administration of a PTH suppressant will also initially suppress the PTH antagonist level. However, as the PTH suppressant dosage increases, the level of PTH antagonist will reach a minimal level and then start to increase before the level of PTH agonist stops decreasing. To avoid inducing ALBT in such patients, the administration of PTH suppressant should be adjusted so that the PTH antagonist level reaches and stays about the minimal level mentioned above. Ordinarily skilled artisans know that this level may vary from patient to patient, but can determine what is best for a particular patient through monitoring the PTH level response to therapy.

[0042] Preferably, PTH agonist levels are measured directly using an assay that does not detect PTH antagonist either in blood, plasma, or serum. For example, Scantibodies Laboratory Whole PTH Assay or Scantibodies Laboratory CAP Assay are appropriate assays.

[0043] PTH antagonist levels should be measured using an assay that either directly detects PTH antagonist (but not PTH agonist) or indirectly through a total PTH measurement that measures the sum of the PTH agonist and PTH antagonist. An indirect measurement subtracts the PTH agonist value from the total PTH value, deriving the PTH antagonist value.

- 5 Thus, one should use a total PTH assay that is designed to have essentially 100% cross-reactivity with PTH antagonist and PTH agonist. For example, Scantibodies Laboratory Total Intact PTH Assay or Scantibodies Laboratory Intact PTH Assay are appropriate assays.

- [0044] The present method should be used when a PTH suppressant type therapy is used. Applicable treatments include calcium administration, vitamin D and vitamin D
10 analogue administration, and calcimimetic administration. For untreated ESRD patients, the therapeutic should be administered in increasing increments from an amount nominal for the selected PTH suppressant. If the patient is already receiving PTH suppressant type therapy, one can terminate the therapeutic administration for a time sufficient to allow the patient to return to a relatively non-suppressed state. The time it takes to return to a relatively non-
15 suppressed state may range from about 3 to 5 minutes to about 20 minutes up to about three to about six months.

- [0045] The relatively non-suppressed state may either account for parathyroid gland status and/or bone status. For example, without being bound by theory, a person may return to a relatively non-suppressed state with respect to the parathyroid gland status in about 3 to
20 about 5 minutes, frequently ranging up to about 20 minutes. This is because the PTH levels in a patient, with respect to parathyroid gland status, may change within minutes of a change in the dose of PTH suppressant, and a return to a relatively non-suppressed state might be considered to occur within minutes. Often times, the return to a relatively non-suppressed state, with respect to the parathyroid gland status, may range from about 10 minutes up to one
25 or more hours or days. Also, for example, without being bound by theory, a person may return to a relatively non-suppressed state with respect to the bone status in about 3 weeks to about 6 months, frequently ranging between about 3 to about 6 months. This range may be 3 months, about 4 months, about 5 months or about 6 months. Often times, the return to a relatively non-suppressed state may range from about 3 or about 4 weeks to about 6 weeks.
30 Also, frequently the time it takes to return to a relatively non-suppressed state may be measured in days or similar increments within the larger range of weeks or months, e.g., between about one to about 6 or about 7 days within a week span.

[0046] As an alternative to discontinuing PTH type suppressant therapy, if a patient is already receiving PTH type suppressant therapy, one can adjust the amount of therapeutic, up

or down, until the level of PTH antagonist is minimized. Frequently, one would take the PTH agonist level into account while adjusting therapeutic to minimize the level of PTH antagonist. The administering physician can easily determine the appropriate dosage on a patient-by-patient basis. The skilled artisan appreciates that the change in dosage for PTH suppressant may differ from that of another. However, the physician can always be guided by the present procedure to affect the best compromise for each individual patient between PTH over-suppression and abnormally elevated PTH.

C. Parathyroid Hormone Antagonists

[0047] In general, a PTH antagonist of the present invention comprises a contiguous portion of human PTH having an amino acid sequence set forth in SEQ ID NO:1 (PTH₁₋₈₄), or a nucleic acid encoding said portion of human PTH, and said PTH antagonist has the following characteristics: a) the N-terminal amino acid residue of said PTH antagonist starts at any position spanning position 2 through position 33 of said PTH₁₋₈₄; b) the C-terminal amino acid residue of said PTH antagonist ends at any position spanning position 35 through position 84 of said PTH₁₋₈₄; and c) said PTH antagonist has a minimal length of three amino acid residues. Preferably, the PTH antagonist is in the form of a pharmaceutical composition, which pharmaceutical composition comprises an effective amount of the PTH antagonist and a pharmaceutically acceptable carrier or excipient.

[0048] The N-terminal amino acid residue of the PTH antagonist can start at any position spanning position 2 through position 33 of said PTH₁₋₈₄. For example, the N-terminal amino acid residue of the PTH antagonist can start at position 2 of the PTH₁₋₈₄. The C-terminal amino acid residue of said PTH antagonist can end at any position spanning position 35 through position 84 of said PTH₁₋₈₄. For example, the C-terminal amino acid residue of the PTH antagonist can end at position 84 of the PTH₁₋₈₄.

[0049] In a specific embodiment, the PTH antagonist is a protein or a peptide, or a nucleic acid encoding said protein or peptide, selected from the group consisting of PTH₂₋₈₄, PTH₃₋₈₄, PTH₄₋₈₄, PTH₅₋₈₄, PTH₆₋₈₄, PTH₇₋₈₄, PTH₈₋₈₄, PTH₉₋₈₄, PTH₁₀₋₈₄, PTH₁₁₋₈₄, PTH₁₂₋₈₄, PTH₁₃₋₈₄, PTH₁₄₋₈₄, PTH₁₅₋₈₄, PTH₁₆₋₈₄, PTH₁₇₋₈₄, PTH₁₈₋₈₄, PTH₁₉₋₈₄, PTH₂₀₋₈₄, PTH₂₁₋₈₄, PTH₂₂₋₈₄, PTH₂₃₋₈₄, PTH₂₄₋₈₄, PTH₂₅₋₈₄, PTH₂₆₋₈₄, PTH₂₇₋₈₄, PTH₂₈₋₈₄, PTH₂₉₋₈₄, PTH₃₀₋₈₄, PTH₃₁₋₈₄, PTH₃₂₋₈₄, and PTH₃₃₋₈₄. In another specific embodiment, the PTH antagonist is a protein or a peptide, or a nucleic acid encoding said protein or peptide, selected from the group consisting of PTH₇₋₆₉, PTH₇₋₇₀, PTH₇₋₇₁, PTH₇₋₇₂, PTH₇₋₇₃, PTH₇₋₇₄, PTH₇₋₇₅, PTH₇₋₇₆, PTH₇₋₇₇, PTH₇₋₇₈, PTH₇₋₇₉, PTH₇₋₈₀, PTH₇₋₈₁, PTH₇₋₈₂, PTH₇₋₈₃ and PTH₇₋₈₄.

[0050] The PTH antagonist can have any suitable length provided that it maintains its antagonizing activity. For example, the PTH antagonist can have a length of 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82 or 83 amino acid residues.

D. Parathyroid Hormone Agonists

[0051] In general, a PTH agonist of the present invention comprises a contiguous portion of human PTH having an amino acid sequence set forth in SEQ ID NO:1 (PTH₁₋₈₄), and the PTH agonist has the following characteristics: a) the N-terminal amino acid residue of the PTH agonist starts at position 1 of the PTH₁₋₈₄; and b) the C-terminal amino acid residue of the PTH agonist ends at any position spanning position 34 through position 84 of the PTH₁₋₈₄.

[0052] Without being bound by theory, the N-terminal amino acid residue of the PTH agonist generally starts at position 1 of said PTH₁₋₈₄. For example, the N-terminal amino acid residue of the PTH agonist can start at position 1 of the PTH₁₋₈₄. The C-terminal amino acid residue of said PTH agonist can end at any position spanning position 34 through position 84 of said PTH₁₋₈₄. For example, the C-terminal amino acid residue of the PTH agonist can end at position 84 of the PTH₁₋₈₄.

[0053] The PTH agonist can have any suitable length provided that it maintains its agonizing activity. For example, the PTH agonist can have a length of 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82 or 83 amino acid residues.

[0054] The present invention is further described by the following examples. The examples are provided solely to illustrate the invention by reference to specific embodiments. These exemplifications, while illustrating certain specific aspects of the invention, do not portray the limitations or circumscribe the scope of the disclosed invention.

E. Kits

[0055] The invention also provides for kits for carrying out the methods of the invention. Such kits comprise in one or more containers a means for determining and monitoring the level of parathyroid hormone (PTH) agonist in a renal patient having secondary hyperparathyroidism; in one or more containers, a means for determining and monitoring the level of PTH antagonist in the patient alone or in combination with other

agents; and a means for administering a therapeutic to the patient that suppresses PTH agonist whereby the amount of therapeutic administered is adjusted such that PTH agonist levels are decreased and the level of PTH antagonist is minimized. Examples of means for determining and monitoring PTH agonist levels in a patient comprise a variety of PTH assays further
5 described herein. And, examples of means for determining and monitoring PTH antagonist levels in a patient comprise a variety of PTH assays further described herein. Preferred forms may be in combination with sterile saline, dextrose solution, or buffered solution, or other pharmaceutically acceptable sterile fluid. Alternatively, useful therapeutic compositions may be lyophilized or dessicated; in this instance, the kit optionally further comprises in a
10 container a pharmaceutically acceptable solution, preferably sterile, to reconstitute the complex to form a solution for injection purposes. Exemplary pharmaceutically acceptable solutions are saline and dextrose solution.

[0056] In one aspect, a kit of the invention further comprises a needle or syringe as a means for administering a therapeutic to a patient, preferably packaged in sterile form, for
15 injecting the composition, and/or a packaged alcohol pad. Instructions are optionally included for administration of composition by a physician or by the patient.

[0057] Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

[0058] The present invention is further described by the following examples. The
20 examples are provided solely to illustrate the invention by reference to specific embodiments. These exemplifications, while illustrating certain specific aspects of the invention, do not portray the limitations or circumscribe the scope of the disclosed invention.

EXAMPLES

EXAMPLE 1

25 [0059] A clinical trial was held for ninety ESRD patients. Each patient had been receiving vitamin D suppressant therapy in accordance with the manufacturer's guidelines. Each patient was removed from the therapy for a washout period of four weeks, and this was confirmed by a rise in PTH measurements after removal of the therapeutic. PTH maxacalcitol (made by Chugai Pharmaceutical Corporation of Tokyo, Japan) suppressant
30 therapy was started after the washout at a constant administration of 5.5 µg intravenously every three days. Blood samples were obtained from each patient after the washout (week 0), six weeks after therapy restart (week 6), and twelve weeks after therapy restart (week 12). The samples were assayed for PTH agonist levels and PTH antagonist levels using the PTH

agonist assay and total PTH assay made by Scantibodies Laboratory, Inc. The samples were assayed for bone specific alkaline phosphatase using a commercially available immunoassay from Hybritech, Inc. of San Diego, California.

Clinical Results

- 5 [0060] The results of the assays for the ninety patients are shown in FIGURE 2 and the following table as median values:

TABLE

<i>Parameter</i>	<i>Time</i> <i>0 Weeks</i>	<i>Time</i> <i>6 weeks</i>	<i>Time</i> <i>12 weeks</i>
Total PTH pg/ml	886	531 (41% decrease)	525 (1% decrease)
PTH agonist pg/ml	609	361 (41% decrease)	331 (8% decrease).
PTH antagonist pg/ml	276	160 (42% decrease)	194 (21% increase)
Alkaline Phosphatase U/ml	396	344 (13% decrease)	290 (16% decrease)

- [0061] The Table shows how the PTH suppressant lowered both the PTH agonist and
- 10 the total PTH values. After six weeks, the PTH agonist and the total PTH values have decreased by 41%. However, after twelve weeks, these values have decreased a mere 8% (PTH agonist) and 0.8% (total PTH). These results indicate that the PTH suppressant is having difficulty driving the PTH agonist levels down any further. Moreover, the levels of total PTH and PTH agonist are still commonly regarded as being above normal levels (of less
- 15 than 37 pg/ml for PTH agonist and less than 65 pg/ml for total PTH, see, e.g., Nussbaum SR, et al., "Highly sensitive two-site immunoradiometric assay of parathyrin, and its clinical utility in evaluating patients with hypercalcemia," Clin. Chem. 1987; 33:1364-67) for non-ESRD patients.

[0062] The Table provided above indicates the difference in response of PTH antagonist to the PTH suppressant versus the total PTH and PTH agonist response. After six weeks, the PTH antagonist level has decreased by 42%, consistent with the PTH agonist levels after six weeks. However, after twelve weeks, the PTH antagonist level increases by 21%, in contrast to PTH agonist levels. The continued use of PTH suppressant at this level will elevate the PTH antagonist levels. Over a period of time, the increase in PTH antagonist levels will lead to ALBT and subsequent vascular calcification (as confirmed in the Table by the further drop in alkaline phosphatase at twelve weeks). These patients need to have the PTH suppressant dosage lowered to maintain the PTH antagonist at a minimal (in this case 160 pg/ml) level. The medical benefit realized in reducing the PTH agonist level beyond a particular level, even by a small percentage, is far outweighed by the harm caused by the resulting elevation of the PTH antagonist level. This rise in the PTH antagonist level may cause ALBT by inhibiting osteoclast formation, a necessary component in healthy bone modeling involving bone resorption and bone turnover.

15 EXAMPLE 2

[0063] To verify that PTH agonist and PTH antagonist concentrations and the PTH agonist/antagonist ratio accurately discriminate between high and low bone turnover in renal patients, bone biopsy data is obtained from renal patients having secondary hyperparathyroidism. See Faugere, M-C, et. al., Kidney Int'l. 2001; 60:1460-68. Bone biopsy data will also verify that calculation and evaluation of both PTH agonist and PTH antagonist level data in renal patients provides a more useful therapeutic and prognostic indicator than evaluation of PTH agonist data alone.

Experimental Design

[0064] Patients with a total PTH greater than 200 pg/ml (as measured by an Intact PTH assay), will have PTH agonist and PTH antagonist levels and the PTH agonist/antagonist ratio determined by Scantibodies® CAP PTH assay (PTH agonist), Scantibodies® Whole PTH assay (PTH agonist), Scantibodies® total intact PTH assay (total PTH) and/or Scantibodies® intact PTH assay (total PTH). Those with a total PTH level greater than 400 pg/ml, or between 200-400 pg/ml, and a PTH agonist/antagonist ratio less than 1.5 will undergo double tetracycline bone labeling and outpatient percutaneous needle biopsy of the pelvic crest bone, under local anesthesia.

[0065] These patients will also have their bone specific alkaline phosphatase and TRAP (tartrate resistant acid phosphatase) measured through known means. In addition, x-

ray data will be obtained from each patient through the use of mamographic x-ray techniques known in the art.

Patient Population & Selection Criteria

5 [0066] A large cross-section of hemodialysis and peritoneal dialysis patients will be evaluated in this study. All dialysis patients will be included in the initial patient population selection. However, exclusion criteria includes patients that are generally considered too ill to participate in the study, those whose anticoagulation cannot be discontinued for about 48 to 72 hours, and those that are unable to cooperate with study requirements. At least 30 to 50 percent of the dialysis population is likely to have PTH values in the range required to be
10 considered for bone biopsy.

Results

[0067] Bone biopsy results are correlated with results of the PTH level assays to verify the accuracy of the PTH agonist/antagonist ratio, versus the PTH agonist measurement alone, in determining a patient's bone turnover rate. Biochemical and radiological data are
15 used to verify these results. As known clinical co-morbidities and therapies have an effect on bone turnover, the effects of these are taken into account in evaluating the data.

[0068] The bone biopsy data confirm the efficacy of the PTH agonist/antagonist level comparison and therapy is guided based on a comparison of PTH agonist levels with PTH antagonist levels. Therapy is provided to reduce PTH agonist levels and to minimize PTH
20 antagonist levels in the patients.

[0069] After twelve months, biochemical and radiological parameters are reanalyzed, and repeat bone biopsies are performed in order to assess the clinical benefit of the PTH agonist/antagonist ratio analysis approach.

25 [0070] The above examples are included for illustrative purposes only and are not intended to limit the scope of the invention. Many variations to those described above are possible. Since modifications and variations to the examples described above will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

30 [0071] Citation of the above publications or documents is not intended as an admission that any of the foregoing is pertinent prior art, nor does it constitute any admission as to the contents or date of these publications or documents.

CLAIMS

1 CLAIM:

1. A method for monitoring and guiding therapeutic suppression of parathyroid hormone in
5 renal patients having secondary hyperparathyroidism comprising:
 - a) determining and monitoring the level of a parathyroid hormone (PTH) agonist in a renal patient having secondary hyperparathyroidism;
 - b) determining and monitoring the level of a PTH antagonist in the patient; and
 - c) administering a therapeutic to the patient that suppresses PTH agonist whereby the
10 amount of therapeutic administered is adjusted such that PTH agonist levels are decreased and the level of PTH antagonist is minimized.
2. The method of Claim 1, wherein the therapeutic is administered in increasing increments
15 from a nominal amount.
3. The method of Claim 1, wherein the patient is already receiving the therapeutic, also comprising adjusting the amount of therapeutic until the level of PTH antagonist is minimized.
- 20 4. The method of Claim 1, wherein the therapeutic administration is selected from the group consisting of vitamin D or vitamin D analogue treatment, calcium treatment, or calcimimetic administration.
5. The method of claim 4, wherein the Vitamin D analogue is comprised of paricalcitol,
25 calcitriol, maxacalcitol, alfacalcidol, calcifediol, or ergocalciferol.
6. The method of claim 1, wherein steps a) and b) are performed using a sample obtained from a renal patient.
- 30 7. The method of claim 6, wherein the sample is selected from the group consisting of a serum, a plasma and a blood sample.
8. The method of claim 1, wherein the PTH agonist level is compared with the PTH

antagonist level.

9. The method of claim 1, wherein the PTH antagonist level is determined by subtracting the PTH agonist level from the total parathyroid hormone level.

5

10. The method of claim 1, wherein the PTH agonist level is compared with the total parathyroid hormone level.

11. The method of claim 1, wherein the PTH antagonist level is compared with the total
10 parathyroid hormone level.

12. The method of claim 1, wherein the PTH agonist level is compared with the PTH antagonist level in the form of a ratio or proportion.

13. The method of claim 1, wherein the hyperparathyroidism is caused by chronic renal failure.

14. The method of claim 1, wherein the PTH agonist level and the PTH antagonist level are determined using an immunoassay.

20

15. The method of claim 14, wherein the PTH agonist level is determined using an antibody that distinguishes PTH agonist from PTH antagonist.

16. The method of claim 14, wherein the PTH antagonist level is determined using an
25 antibody that distinguishes PTH agonist from PTH antagonist.

17. The method of claim 1, further comprising monitoring for vascular calcification in the patients.

18. The method of claim 17, wherein the vascular calcification is monitored by monitoring alkaline phosphatase level.

19. The method of Claim 1, wherein the patient is already receiving the therapeutic, also comprising terminating the therapeutic administration for a time sufficient to allow the

patient to return to at least a relatively non-suppressed state.

20. The method of claim 19, wherein the time sufficient to allow the patient to return to at least a relatively non-suppressed state is between about three months to about six months.

5

21. The method of claim 19, wherein the time sufficient to allow the patient to return to at least a relatively non-suppressed state is about three minutes to about twenty minutes.

22. The method of claim 1, wherein the PTH agonist comprises a contiguous portion of human PTH having an amino acid sequence set forth in SEQ ID NO:1 (PTH₁₋₈₄), and the PTH agonist has the following characteristics:

- a) the N-terminal amino acid residue of the PTH agonist starts at position 1 of the PTH₁₋₈₄; and
- b) the C-terminal amino acid residue of the PTH agonist ends at any position spanning position 34 through position 84 of the PTH₁₋₈₄.

15

23. The method of claim 1, wherein the PTH agonist is a peptide having an amino acid sequence of human PTH₁₋₈₄.

20 24. The method of claim 1, wherein the PTH antagonist comprises a contiguous portion of human PTH having an amino acid sequence set forth in SEQ ID NO:1 (PTH₁₋₈₄), and the PTH antagonist has the following characteristics:

- a) the N-terminal amino acid residue of the PTH antagonist starts at any position spanning position 2 through position 33 of the PTH₁₋₈₄;
- b) the C-terminal amino acid residue of the PTH antagonist ends at any position spanning position 35 through position 84 of the PTH₁₋₈₄; and
- c) the PTH antagonist has a minimal length of three amino acid residues.

25

25. The method of claim 1, wherein the PTH antagonist is a peptide having an amino acid sequence of human PTH₇₋₈₄.

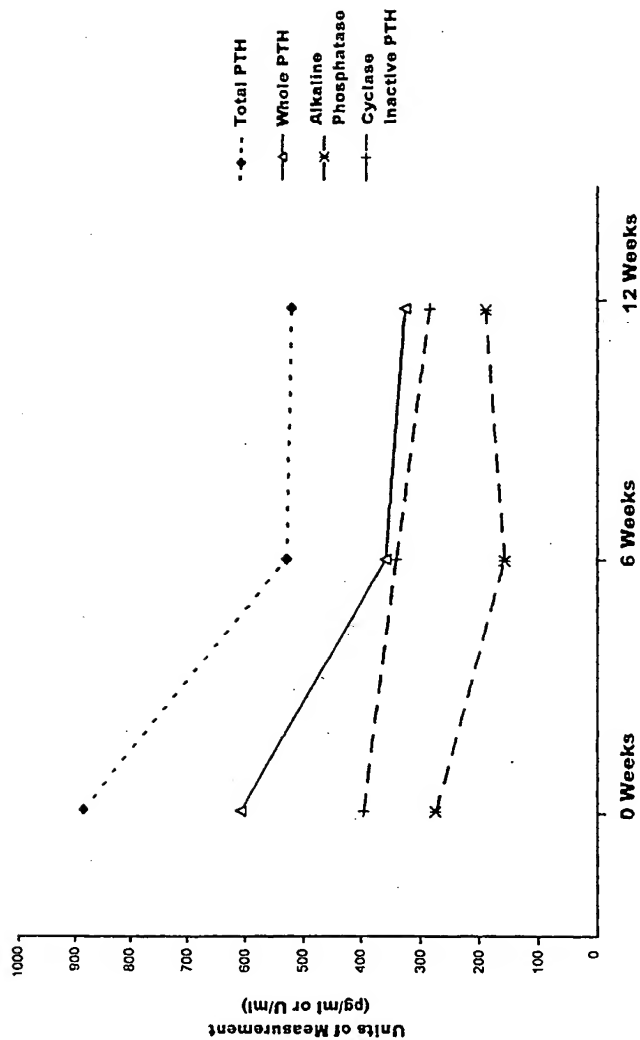
30

26. The method of claim 1, wherein the PTH agonist level and the PTH antagonist level determinations are compared with bone biopsy data.

27. The method of claim 26, wherein the PTH agonist level and the PTH antagonist level determinations are compared with bone biopsy data after administration of the therapeutic.
28. The method of claim 12, wherein the ratio or proportion determination is compared with
5 bone biopsy data.
29. A method for monitoring and guiding therapeutic suppression of parathyroid hormone in renal patients having secondary hyperparathyroidism comprising:
- a) obtaining a sample from a renal patient having secondary hyperparathyroidism;
 - 10 b) determining and monitoring the level of a parathyroid hormone (PTH) antagonist in the renal patient; and
 - c) administering a therapeutic to the patient capable of suppressing a PTH agonist, whereby the amount of therapeutic administered is adjusted such that the level of PTH antagonist is minimized in the patient.
- 15 30. The method of Claim 29, wherein the therapeutic is administered in increasing increments from a nominal amount.
31. The method of Claim 29, wherein the therapeutic administration is selected from the
20 group consisting of vitamin D or vitamin D analogue treatment, calcium treatment, or calcimimetic administration.
32. The method of claim 31, wherein the Vitamin D analogue is comprised of paricalcitol, calcitriol, maxacalcitol, alfacalcidol, calcifediol, or ergocalciferol.
- 25 33. The method of claim 29, further comprising monitoring for vascular calcification in said patients.
34. The method of claim 33, wherein vascular calcification is monitored by monitoring
30 alkaline phosphatase levels.
35. The method of Claim 29, wherein the patient is already receiving the therapeutic, also comprising terminating the therapeutic administration for a time sufficient to allow the patient to return to at least a relatively non-suppressed state.

36. The method of claim 35, wherein the time sufficient to allow the patient to return to at least a relatively non-suppressed state is between about three months to about six months.
- 5 37. The method of claim 35, wherein the time sufficient to allow the patient to return to at least a relatively non-suppressed state is about three minutes to about twenty minutes.
38. The method of claim 29, wherein the PTH antagonist level is determined through determining and compared with the total PTH level with the PTH agonist level.
- 10 39. A kit useful for monitoring and guiding therapeutic suppression of parathyroid hormone in renal patients having secondary hyperparathyroidism comprising:
- a) means for monitoring the level of parathyroid hormone (PTH) agonist in a renal patient having secondary hyperparathyroidism;
 - 15 b) means for monitoring the level of PTH antagonist in the patient; and
 - c) means for administering a therapeutic to the patient that suppresses PTH agonist whereby the amount of therapeutic administered is adjusted such that PTH agonist levels are decreased and the level of PTH antagonist is minimized.
- 20 40. The kit of Claim 39, wherein the therapeutic administration is selected from the group consisting of vitamin D or vitamin D analogue treatment, calcium treatment, or calcimimetic administration.
41. The kit of claim 40, wherein the Vitamin D analogue is comprised of paricalcitol,
- 25 calcitriol, maxacalcitol, alfacalcidol, calcifediol, or ergocalciferol.
42. The kit of claim 39, further comprising instructions for use.

FIG. 2



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/35516

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 38/00, 38/16, 31/59; G01N 33/53

US CL : 514/12, 167; 435/7.1; 424/198.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/12, 167; 435/7.1; 424/198.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST, STN/MEDLINE.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JOHN et al, A novel immunoradiometric assay detects full-length human PTH but not amino-terminally truncated fragments: implications for PTH measurements in renal failure. Journal of Clinical Endocrinology and Metabolism, 1999, Vol. 84, pages 4287-4290. Especially page 4287, third paragraph of right column; Fig. 1; page 4290, middle of second paragraph of left column.	1-42
Y	MONIER-FAUGERE et al, Improved assessment of bone turnover by the PTH-(1-84)/large C-PTH fragments ratio in ESRD patients. Kidney International, October of 2001, Vol. 60, pages 1460-1468. Especially left column of page 1460; fifth paragraph of left column of page 1462; top of left column of page 1466.	1-42

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

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A document member of the same patent family

Date of the actual completion of the international search

16 December 2002 (16.12.2002)

Date of mailing of the international search report

07 JAN 2003

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